

REMARKS

The third supplemental sequence listing submitted herewith supercedes all previously submitted sequence listings. The sequence listing is provided in paper and computer readable form pursuant to 37 C.F.R. §§ 1.821-1.825. The CRF copy of the sequence listing is provided in ASCII text, in a document labeled "09-218,913 Sequence Listing," on a diskette labeled "09-218,913 Sequence Listing." In accordance with 37 C.F.R. § 1.821(f), the sequence listing information recorded in computer readable form is identical to the written (paper copy) sequence listing enclosed herewith. Moreover, the submission of the sequence listing adds no new matter to the application. In addition, the specification is amended to bring it into conformity with the sequence listing. The amendments to the specification do not add new matter.

The new sequence listing corrects errors in several of the sequences appearing in the former sequence listing. The new sequence listing is fully compliant with WIPO Standard ST.25 (1998).

Furthermore, the new sequence listing contains 36 additional sequences that did not appear in the former sequence listing: SEQ ID NO:72-105. These additional sequences were added for two different reasons.

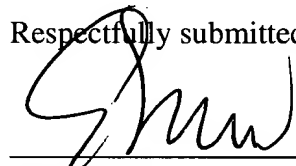
SEQ ID NO:72-74 and 76 were added to comply with the rule prohibiting protein sequences from containing stop codons. The protein sequences shown in Figures 1-3 contain possible stop codons, and were therefore divided into multiple sequences in the new sequence listing. Specifically, the protein sequence shown in Figure 1 is listed as SEQ ID NO:13 and 72; the protein sequence shown in Figure 2 is listed as SEQ ID NO:15, 73, and 74; and the protein sequence shown in Figure 3 is listed as SEQ ID NO:10 and 76.

SEQ ID NO:75 and 77-105 were added to comply with the rule requiring all disclosed sequences to be listed in the sequence listing. Certain nucleic acid sequences disclosed in Figures 3 and 4C were not listed in the former sequence listing and were therefore added. In particular, the nucleic acid sequence appearing in Figure 3 and labeled "R74593 corr." is listed as SEQ ID NO:75; and the nucleic acid sequences appearing in Figure 4C are listed as SEQ ID NO:77-105.

As a consequence of the additional sequences in the new sequence listing, the submission of the new sequence listing requires the amendments to the specification shown above. The amendments to the specification are fully supported by the application as filed and do not add new matter.

Respectfully submitted,

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Appendix A. Revisions of the Replacement Paragraphs in the Specification,
with Markings to Show Changes Made

Page 4, lines 28-34:

Figure 1 depicts the nucleotide sequence of EST R35464 (SEQ ID NO:12) and the translation of this DNA sequence [(SEQ ID NO:13)] (labeled "ORF") which yielded an open reading frame with some sequence similarity to aprotinin. Amino acids 1-110 of the translation correspond to SEQ ID NO:13; amino acids 112-130 correspond to SEQ ID NO: 72. The translation product contains 5 of the 6 cysteines in the correct spacing that is characteristic for Kunitz-like inhibitor domains (indicated in bold). The position normally occupied by the remaining cysteine (at codon 38) contained instead a phenylalanine (indicated by an asterisk).

Page 4, line 35 to page 5, line 4:

Figure 2 depicts the nucleotide sequence of EST R74593 (SEQ ID NO:14), and the translation of this DNA sequence [(SEQ ID NO:15)] (labeled "ORF") which yielded an open reading frame with homology to the Kunitz class of serine protease inhibitor domains. Amino acids 3-22 of the translation correspond to SEQ ID NO:15; amino acids 24-131 correspond to SEQ ID NO:73; amino acids 136-166 correspond to SEQ ID NO:74. The translation product contained 6 cysteines in the correct spacing that is characteristic for Kunitz-like inhibitor domains (indicated in bold). However, this reading frame sequence includes stop codons at codon 3 and 23.

Page 5, lines 5-16:

Figure 3 depicts a deduced nucleic acid sequence of human placental bikunin (SEQ ID NO:9) labeled "consensus" and matched with the translated protein amino acid sequence labeled

“translated” [(SEQ ID NO:10)]. Amino acids –18-179 of the translation correspond to SEQ ID NO:10; amino acids 184-214 correspond to SEQ ID NO:76. Also as comparison are shown the nucleic acid sequence for ESTs H94519 (SEQ ID NO:16), N39798 (SEQ ID NO:17), R74593 [(SEQ ID NO:14)] (corrected by the insertion of G at position 114) (SEQ ID NO:75) and R35464 (SEQ ID NO:12). The underlined nucleotides in the consensus sequence correspond to the site of PCR primers described in the Examples. Underlined amino acids in the translated consensus sequence are residues whose identity have been confirmed by amino acid sequencing of purified native human placental bikunin. Nucleotide and amino acid code are standard single letter code, “N” in the nucleic acid code indicates an unassigned nucleic acid, and “*” indicates a stop codon in the amino acid sequence.

Page 6, lines 27-34:

Figure 4C depicts the corresponding alignment of the oligonucleotide sequences of each of the overlapping ESTs shown schematically in Figure 4B. The upper sequence (SEQ ID NO:51) labeled bikunin represents the consensus oligonucleotide sequence derived from the overlapping nucleotides at each position. The numbers refer to base-pair position within the EST map. The oligonucleotides in EST R74593 (SEQ ID NO:89) that are bold underlined (at map positions 994 and 1005) are base insertions observed in R74593 that were consistently absent in each of the other overlapping ESTs. In Figure 4C, N40851 corresponds to SEQ ID NO:77; N39876 corresponds to SEQ ID NO:78; R87894 corresponds to SEQ ID NO:79; H16866 corresponds to SEQ ID NO:80; R34808 corresponds to SEQ ID NO:81; T66058 corresponds to SEQ ID NO:82; N57450 corresponds to SEQ ID NO:83; N57374 corresponds to SEQ ID NO:84; R35464 corresponds to SEQ ID NO:85; H94519 corresponds to SEQ ID NO:86; N39798

corresponds to SEQ ID NO:87; H87300 corresponds to SEQ ID NO:88; R74593 corresponds to
SEQ ID NO:89; R31730 corresponds to SEQ ID NO:90; R34701 corresponds to SEQ ID NO:91;
H02982 corresponds to SEQ ID NO:92; R32676 corresponds to SEQ ID NO:93; T47439
corresponds to SEQ ID NO:94; R73968 corresponds to SEQ ID NO:95; H39840 corresponds to
SEQ ID NO:96; H95233 corresponds to SEQ ID NO:97; H39841 corresponds to SEQ ID NO:98;
N30199 corresponds to SEQ ID NO:99; T52966 corresponds to SEQ ID NO:100; N29508
corresponds to SEQ ID NO:101; N26919 corresponds to SEQ ID NO:102; N26910 corresponds
to SEQ ID NO:103; H16757 corresponds to SEQ ID NO:104; and N27732 corresponds to SEQ
ID NO:105.